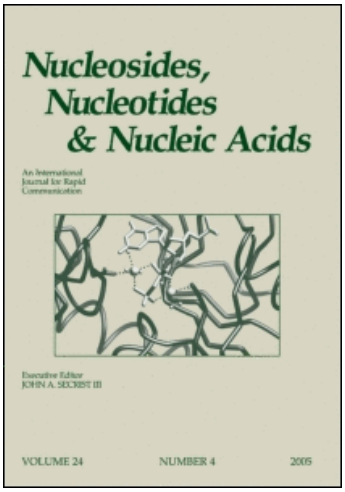

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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To cite this Article Cheng, Vera , Hughes, Lawrence , Griffin, Vivian B. , Montserret, Roland and Ollapally, Abraham P.(1986) 'Synthesis of 1-(4-*Keto*-2, 3-*O*-isopropylidene-α-L-rhamnopyranosyl) uracil', Nucleosides, Nucleotides and Nucleic Acids, 5: 2, 223 — 228
To link to this Article: DOI: 10.1080/07328318608068675
URL: http://dx.doi.org/10.1080/07328318608068675

NUCLEOSIDES & NUCLEOTIDES, 5(2), 223-228 (1986)

NOTE

SYNTHESIS OF 1-(4-KETO-2,3-O-ISOPROPYLIDENE-α-L-RHAMNOPYRANOSYL)URACIL

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Abstract: Synthesis of 1-(2,3,4-tri-O-acetyl-α-L-rhamnopyranosyl)uracil (3), 1-(α-L-rhamnopyranosyl)uracil (4), 1-(2,3-O-isopropylidene-α-L-rhamnosyl)uracil (5), and 1-(2,3-O-isopropylidene-4-keto-α-L-rhamnopyranosyl)uracil (6) are reported. Oxidation of (5) to (6) was effected using pyridinium chlorochromate in presence of molecular sieves.

We have undertaken the synthesis of the title compound with the intention of converting it to 1-(4-keto-α-L-rhamnopyranosyl)uracil to compare the biological activity of this with 4'-keto-rhamnopyranosyl nucleosides of C-5 halogen (F,Cl,Fr) substituted uracils and 6-azauricl. We have reported the synthesis of 5-chloro-1-(4-keto-2,3-O-isopropylidene-α-L-rhamnosyl)uracil[1]. Other syntheses are in progress. These syntheses were prompted by the observation made by Antonakis and associates[2-4] that keto nucleosides of L-rhamnose and L-fucose with theophylline and 6-chloropurine showed anticancer properties against KB cells and leukemia L-1210. We wanted to investigate whether naturally occurring pyrimidine bases, as well as modified bases, exhibit the same or enhanced biological activity.

Our attempts to prepare pure deacetonated ketonucleosides have been unsuccessful. We have tried the following procedures, (a) nitromethane-

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methanol 9:1(v/v) with concd. H_2SO_4[5], (b) trifluoracetic acid-methanol 9:1(v/v)[6] and (c) stirring with Rexyn IR-120[H^+][7]. Methods (b) and (c) gave identical mixtures of two ketonucleosides in the ration 1:1[^{1}H NMR]. Separation of these compounds was difficult due to the close proximity of their R_f values.

As previously observed[8], we have found an inversion of conformation of the sugar. The high coupling constants J_{Hz}1',2' for (3), (4) and (5) show these have $^4C_1$ conformation. On introducing the carbonyl group at C-4', the coupling constant J_{Hz}1',2' is reduced to 2Hz, for (6) indicative of a conformation $^1C_4$.

Experimental Section

Melting points (uncorrected) were determined using Mel Temp apparatus. Thin layer chromatography (TLC) was done on precoated silica gel plastic sheets 60 F_{254} (0.2 mm) EM Reagents. Compounds were detected under short wave UV light. Sugar was detected by spraying with 3% concd. H_2SO_4 in ethanol (v/v) and heating the plastic strips by a heat gun. Ethyl acetate was used throughout as the eluant for TLC. Optical rotation was determined using Model SR6 polarimeter from PolyScience Corporation. Proton magnetic Resonance (^{1}H NMR) spectra were recorded by a Brüker/IBM SY200. Ethyl acetate and dichloromethane used in the oxidation step were distilled and stored in all-glass containers over 4Å molecular sieves (MS) at least for a week before use. 3Å MS used for oxidation were finely powdered and heated to about 375°C, just before the experiment, in vacuum, in the vicinity of P_2O_5 in the cold sleeve of a specially designed tube. MS were cooled to ambient temperature in the tube before adding to the reaction mixture. Column chromatography was done using silica gel, Kieselgel 60 (70-230 mesh ASTM).

1,2,3,4-Tri-O-acetyl-α-L-rhamnopyranose(1)

To 100 g (0.61 mol) of α-L-rhamnose, 350 mL of acetic anhydride (3.70 mol) and 250 mL of pyridine (3.09 mol) were added, keeping the reaction flask well cooled in crushed ice, at least for the first forty minutes after mixing the solvents and the sugar. Then the flask was left at room temperature. phase, washed once with water, dried over anhydrous Na_2SO_4,and evaporated to dryness in vacuo. The solid product (3) was dissolved in a minimum quantity of ethyl acetate or absolute ethanol and allowed to crystallize in a refrigerator. Yield 75.8 g (44.2%); mp 98°C; $[\alpha]_D^{20}$ = + 9.50° (c,0.1 methanol); R_f 0.60. Anal. calcd. for $C_{16}H_{20}O_9N_2$: C, 50.00; H, 5.24;

N, 7.29; Found: C, 49.84; H, 5.36; N, 7.20. ^{1}H NMR (DMSO-d_6) δ 6.04 (d,$J_{1',2'}$ = 8 Hz, H-1'); δ 5.4(m,$H_{2',3'}$); δ 4.29(q,$J_{5',6'}$ = 7 Hz, H-5').

1-(α-L-rhamnopyranosyl)uracil RU (4)

23.71 g (0.062 mol) of (3) was dissolved in minimum quantity of absolute methanol. This solution was cooled in crushed ice and saturated with NH_3. Deacetylation was complete by overnight as shown by TLC. The solution was evaporated to dryness in vacuo and compound (4) crystallized from methanol). Yield 15.33 g (96%); mp 209°C; $[\alpha]_D^{20}$ = -35.00°(c, 0.10 methanol); R_f 0.10. Anal. calcd. for $C_{10}H_{14}O_6N_2$: C, 46.40; H, 5.46; N, 10.85; Found: C, 46.60; H, 5.51; N, 10.73. ^{1}H NMR(MeOH-d_4) δ 6.05 (d,$J_{1',2'}$ = 9.5 Hz, H-1'); δ 4.0(q,$J_{2',3'}$ = 3.5 Hz, H-2'); δ 4.07 (q,$J_{3',4'}$ = 3.5 Hz, H-3'); δ 3.74(q,$J_{4',5'}$ = 1.3 Hz, H-4'); δ 4.07 (m, H-5'); δ 1.5 (d,$J_{5',6'}$ = 7 Hz, H-6', 3H); δ 5.73(d,$J_{5,6}$ = 8 Hz, H-5); δ 7.77(d, H-6).

1-(2,3-O-Isopropylidene-α-L-rhamnopyranosyl)uracil, IRU (5)

14.20 g (0.055 mol) of (4) was dissolved in minimum quantity of absolute acetone. 30 mL of 2,2-dimethoxypropane (6 mol equivalent) was added to the solution, followed by 1 mL of concd. H_2SO_4 as catlyst. The mixture was stirred at room temperature under dry conditions. TLC showed the reaction was complete in 3 hours. The solution was then neutralized with N NaOH, cooled for two hours, and vacuum filtered to remove the precipitated Na_2SO_4. The filtrate was concentrated in vacuo to dryness. IRU was then crystallized from ethyl acetate. Yield 15.64 g (95.4%); mp. 154°C; $[\alpha]_D^{20}$ = -24° (c, 0.5 methanol); R_f 0.48. Anal. calcd. for $C_{13}H_{18}O_6N_2$: C, 52.35; H, 6.08; N, 9.39; Found: C, 51.60; H, 6.22 N, 9.10. ^{1}H NMR (acetone-d_6); δ 5.82 (d,$J_{1',2'}$ = 7 Hz, H-1'); δ 4.65 We have noticed that this serves to moderate the highly exothermic reaction and avoid imparting a brownish tinge to the sugar acetate. The mixture was kept vigorously stirred mechanically. Within approximately two hours, the acetylation was completed as checked by TLC (R_f 0.91 for (1), R_f 0.00 for rhamnose). The solution was concentrated in vacuo between 85-90°C to a viscous mass. This process was repeated two to three times each time after adding 75-100 mL of toluene and thoroughly mixing, to remove the pyridine. The semisolid tetraacetate (1) was used for the coupling as is, or the product was purified occasionally by Kugelrohr distillation.

2,4-Di-O-(trimethylsilyl)uracil (2)

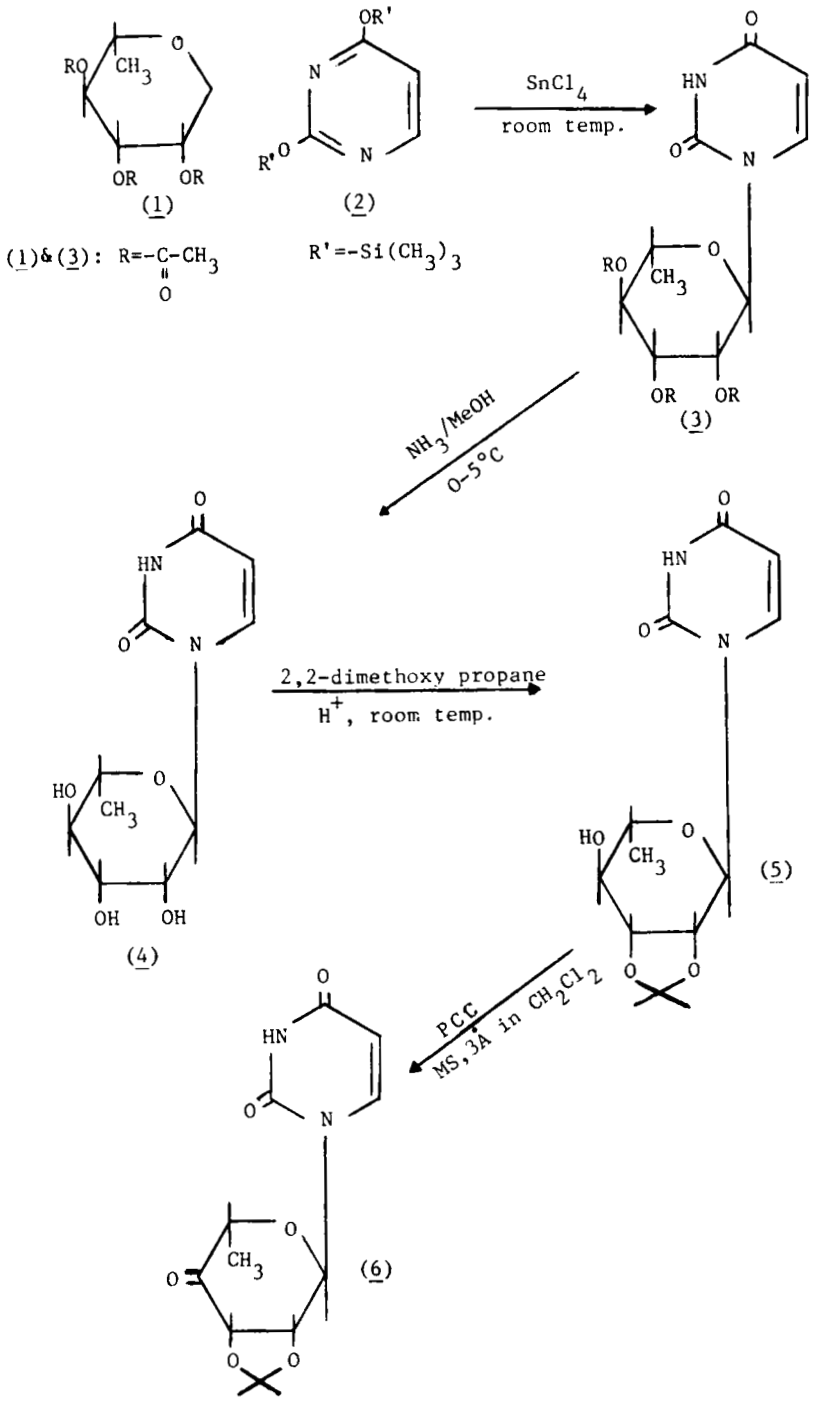
50 g of uracil (0.45 mol) was mixed with 300 mL of absolute 1,2-dichloroethane, 370 mL of hexamethyldisilazane (HMDS) and 1 mL of trimethyl chlorosilane. The mixture was heated under reflux in anhydrous conditions in a silicone oil bath at 135°C. When the uracil was completely dissolved, the bath temperature was lowered to 100°C, and excess of the HMDS and 1,2-dichloroethane was distilled off under reduced pressure, leaving compound (2) in the flask.

1-(2,3,4-Tri-O-acetyl-α-L-rhamnopyranosyl)uracil, TARU (3)

This step was done following essentially the Vorbrüggen and Niedballa method[9] with slight modifications. To the above distilling flask containing 0.45 mol of (2), was added 133.5 g (0.40 mol) of (1), dissolved in about 200 mL of 1,2-dichloroethane. The mixture was cooled well in ice, and to this added in small portions a mixture of 50 mL of $SnCl_4$ (0.43 mol) and 30 mL of absolute 1,2-dichloroethane. Dichloroethane was added to the $SnCl_4$ to avoid excessive fuming during its addition to the reaction mixture. The reaction mixture was kept mechanically stirred at room temperature under anhydrous conditions. The coupling reaction was monitored by TLC, by spraying with H_2SO_4 and heating. The reaction took about 3 hours for completion. The reaction mixture was then diluted with 200 mL of 1,2-dichloroethane and 100 mL of distilled water. This was then neutralized with solid $NaHCO_3$. The precipitated stannic oxide was filtered off under vacuum. The organic layer was separated from the aqueous ($t, J_{2',3'}$ = 6 Hz, H-2'); δ 4.46 ($t, J_{3',4'}$ = 6 Hz, H-3'); δ 3.72 (m, H-4'); δ 3.96 (m, H-5'); δ 1.33 ($d, J_{5',6'}$ = 6.5 Hz, H-6', 3H); δ 5.70 (d); δ 7.74 ($d, J_{5,6}$ = 8 Hz, H-6).

1-(keto-2,3-O-isopropylidene-α-L-rhamnopyranosyl)uracil, KIRU (6)

The oxidation was carried out according to the Herscovici-Antonakis method.[10] 6.43 g (0.22 mol) of (5) was mixed with 11.9 g (0.055 mol) of pyridinium chlorochromate (PCC) and 110 mL of dried dichloromethane. The mixture was stirred well under anhydrous conditions using a drying tube. To this was added 22.0 g of 3Å MS. The progress of the oxidation was monitored by TLC and heating the TLC strip. Compound (6) gave a brown spot on spraying with H_2SO_4 and heating with no spot corresponding to (5). The reaction was complete in 3 h. The solution was then diluted with 200 mL of dry ethyl acetate and stirred for 0.5 h. This was then



vacuum filtered through a bed of silica gel mixed with $CaSO_4$ or Hyflosuper Cel. The filter was washed twice with 100 mL each of absolute ethyl acetate. The filtrate was then concentrated in vacuo to dryness. An oily dark green substance was obtained. The oil was then dissolved in ethyl acetate and purified by column chromatography. The eluate containing the pure (6) was concentrated to dryness and crystallized in ethyl acetate/diethyl ether to give colorless crystals. Yield 4.27 g 90%; mp 175°C; $[\alpha]_D^{20}$ = -20.00°(c,0.10 methanol), R_f 0.61. Anal. Calcd. for $C_{13}H_{16}O_6N_2$: C, 52.70; H, 5.44; N, 9.45; Found: C, 52.57; H, 5.37; N, 9.55: ^1H NMR (acetone d_6) δ 5.47(d,$J_{1',2'}$ = 2 Hz,H-1'); δ 5.04(dd,$J_{2',3'}$ = 7 Hz,H-2'); δ 4.73(d,H-3'); δ 4.36(q,$J_{5',6'}$ = 7 Hz,H-5'); δ 1.36(d,H-6',3H); δ 5.74 (d,H-5); δ 7.90(d,$J_{5,6}$ = 8 Hz,H-6); δ 1.48, isopropylidene).

ACKNOWLEDGEMENT

We are thankful to the National Institutes of Health for financial assistance through the Minority Biomedical Research Support Program, grant number DRR RR08111. Also our sincere thanks to Dr. K. Antonakis and his associates for the timely advice in the course of this work.

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Received August 30, 1985.